A long noncoding RNA protects the heart from pathological hypertrophy.

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Public Summary:
In collaboration with investigators from other institutions, we identify a novel long non-coding RNA (lncRNA), a form of RNA that does not make proteins, in mouse hearts that protects the heart from hypertrophy and heart failure. We first identified a cluster of lncRNA transcripts between two contractile myosin motor genes, Myh6 (α-MHC) and Myh7 (β-MHC) in hearts, and named them MyHEART genes. Among this cluster of MyHEART lncRNA genes, we show that restoring the expression level of MyHEART-779 protects the mouse hearts from hypertrophy and dysfunction. We further show that MyHEART-779 prevents Brg1 (a transcription regulator) from targeting to the promoters of downstream genes of Brg1 by binding to the active helicase core of Brg1, resulting in the down-regulation of pro-hypertrophic effects of Brg1. This inhibitory interaction of MyHEART on Brg1 function is a novel mechanism for how an lncRNA can regulate chromatin function. Our study also establishes a new paradigm in the biochemical basis of how lncRNA antagonizes chromatin regulators to gain control over the chromatin. These new mechanisms regarding how Brg1 recognizes target chromatins are novel and have never been observed or conceived by others working in this field. We believe that these novel mechanisms of lncRNA actions might extend beyond cardiac biology and are applicable to the general area of biology.

Scientific Abstract:
The role of long noncoding RNA (lncRNA) in adult hearts is unknown; also unclear is how lncRNA modulates nucleosome remodelling. An estimated 70% of mouse genes undergo antisense transcription, including myosin heavy chain 7 (Myh7), which encodes molecular motor proteins for heart contraction. Here we identify a cluster of lncRNA transcripts from Myh7 loci and demonstrate a new lncRNA-chromatin mechanism for heart failure. In mice, these transcripts, which we named myosin heavy-chain-associated RNA transcripts (Myheart, or Mhrt), are cardiac-specific and abundant in adult hearts. Pathological stress activates the Brg1-Hdac-Parp chromatin repressor complex to inhibit Mhrt transcription in the heart. Such stress-induced Mhrt repression is essential for cardiomyopathy to develop: restoring Mhrt to the pre-stress level protects the heart from hypertrophy and failure. Mhrt antagonizes the function of Brg1, a chromatin-remodelling factor that is activated by stress to trigger aberrant gene expression and cardiac myopathy. Mhrt prevents Brg1 from recognizing its genomic DNA targets, thus inhibiting chromatin targeting and gene regulation by Brg1. It does so by binding to the helicase domain of Brg1, a domain that is crucial for tethering Brg1 to chromatinized DNA targets. Brg1 helicase has dual nucleic-acid-binding specificities: it is capable of binding lncRNA (Mhrt) and chromatinized-but not naked-DNA. This dual-binding feature of helicase enables a competitive inhibition mechanism by which Mhrt sequesters Brg1 from its genomic DNA targets to prevent chromatin remodelling. A Mhrt-Brg1 feedback circuit is thus crucial for heart function. Human MHRT also originates from MYH7 loci and is repressed in various types of myopathic hearts, suggesting a conserved lncRNA mechanism in human cardiomyopathy. Our studies identify a cardioprotective lncRNA, define a new targeting mechanism for ATP-dependent chromatin-remodelling factors, and establish a new paradigm for lncRNA-chromatin interaction.